REMARKS

The claims that were objected to have been amended to deal with the examiner's objections.

As discussed during the interview with the examiner, the essence of the present invention is to minimize action by acetylcholinesterase inhibitors as specified in the claims during periods of sleep. As suggested by the examiner, submitted herewith is a declaration by the inventor explaining this.

The Examiner has rejected the claims under 35 USC 112, first paragraph, as failing to comply with the written description and enablement requirement. For the purpose of expediting prosecution of the present application and without prejudice to the possibility of filing a divisional application to the subject mater of any claim as presented previously, all claims have been amended to specify that the treatment claimed is for a person suffering from Alzheimer's disease and that the compounds in question are galanthamine, lycoramine, analogs of galanthamine, analogs of lycoramine or rivatsigmine, said analogs being limited to those indicated by the examiner as being acceptable.

It is therefore submitted that the rejection under 35 USC 112 fiirst paragraph has been overcome.

So far as the rejection under 35 USC 112 second paragraph is concerned, "one" has been replaced by "two" where appropriate to avoid the possible interpretation that a methyl group is replacing a methyl group. Claim 41 has been amended as suggested by the examiner

The Examiner has rejected claims 1, 3-5, 7-21, 22, 24-26, and 28-41 under 35 USC 103(a).over 1) WO88/08708; or 2) the combination of WO88/08708 and Moonman U.S. 5,643, 905 or 3) the combination of Shapiro, Moonman and Conte.

There are three independent claims in the application: claim 1 directed to a dosage form that is formulated to delay activity of an Alzheimer's drug for from four to twelve hours; claim 21 directed to a method of treatment in which an Alzheimer's drug formulated to delay action for from four to twelve hours is administered at such a time that the delay in release resulting from use of the specified delay will result in a delay in release until after a period of sleep has occurred; and claim 41 directed to a method of treatment wherein the degree of delay in release and the half life of the drug are balanced so that the drug is administered prior to one period of sleep, the delay in release resulting in the drug not being released during that period and the selection of the half life being such that the dose has been metabolized prior to the next normal period of sleep. In the first two cases it is required that the drug used be one that has a half life of from one to eleven hours. Galanthamine is a typical drug to be used in each case.

As discussed at the interview, there is a difference between the concept of the present invention in which the objective is to avoid the activity of an acetylcholinesteras inhibitor at times when such activity will cause difficulties, in particular interference with sleep and prior art compositions which have had the objective of providing sustained release over a given period. This difference is brought out by the declaration by Dr. Davis submitted herewith.

Turning now to the prior art cited by the Examiner:

WO88/08708 refers to sustained release compositions at page 24 line 12. There is no suggestion that there should be any period during which activity of the compounds should be delayed so that there was no activity, simply that release should be sustained over a period.

Moonman is referred to by the examiner because of its description of the use of galanthamine to promote awakening from "twilight sleep" and its reference to constant and controlled release. Twilight sleep is a condition induced by scopolamine that has been used to ease pain during labor and child birth. It has nothing to do with regular sleep. The reference to controlled release clearly does not contemplate any period in which the objective is zero release as is required by

the present invention. Column 3 lines19 - 30 describes a formulation in which a small hole is present in a semipermeable membrane surrounding the drug so that release is effected by osmotic pressure. There is no delay period during which release will not occur once the capsule is contacted with a liquid. Column 3 lines 31 to 34 describes release from a wax matrix. Again release may be slow. But it is not delayed so as to provide a period in which the objective is no release at all.

Shapiro describes a combination therapy for treating inter allia Alzheimer's disease in which various compounds, including inter alia acetyl cholinesterase inhibitors such as galanthamine may be used in combination with carbonyl trapping agents. There is no suggestion of any particular way in which the compounds should be administered.

Conte teaches that it is possible to make tablets that release drug after "a programmable period of time." This, however, is a very general statement and when Conte comes to be more precise, it is clear (see the end of the second paragraph of the article) that what he has in mind is daily variation in pharmacokinetics and/or drug effects, "depending on physiological and/or physiopathological changes of circadian rhythmicity". This emphasis on circadian rhythmicity is repeated in the following paragraph. The examiner points to column 2 of the first page of the Conte article to suggest that reading Conte's teaching as being confined to dealing with problems associated with circadian rhythms relating to the disease itself is to give it a too limited interpretation. It is respectfully submitted that this is not the case. The only discussion of timing in the column referred to by the examiner is a statement that the tablets Conte describes may be used for "all diseases that show a night symptomatic recrudescence". There is nothing to suggest that there might be any benefit in suppressing release during the night. Indeed what is proposed is exactly contrary to this - release during the night. . . As noted in response to the previous action, Conte gives the examples of asthma and hypertension and states that an asthmatic attack generally happens in the early morning and that in hypertension diseases the pressure value is higher during the daytime. The teaching of Conte is directed to drugs that should be administered at a specific time of day in order to have the most beneficial effect "to

fulfil the specific therapeutic needs of such diseases, which depend on circadian rhythmicity, new drug-delivery devices are required..."

This differs from the invention claimed in this application. As stated as an example in the previous response, Alzheimer's does not have diurnal variation and treatment is not controlled by circadian rhythm. What the present invention does is to take steps to prevent certain effects resulting from the activity of the drug from taking place at a time when they are undesired rather than formulating a product to have positive effects at a desired time. Nothing in the prior art points to such a possibility.

In order for there to be a finding of obviousness based on the combination of two references, there must be a motivation to combine them. No such motivation exists in the present case. Shapiro relates to a combination therapy in which a wide variety of drugs may be used, acetylcholinsterase inhibitors included but gives no indication that their use should be in any way time specific. Conte teaches that if one has drugs whose release should be time specific he has a good way to accomplish this. However, there is nothing to cause one to employ specific acetylcholinesterase inhibitors or acetylcholinesterase inhibitors having a particular half life into Conte's tablets. Nor is there any teaching as to what the "programmable period" referred to by Conte should be if one did choose to put such drugs into one of Conte's tablets. Finally there is no teaching that one should select a combination of half life and time delay to achieve a particular result as is done in present claim 41. It is submitted that the combination of Moonman, Shapiro and Conte can in no way render the invention as claimed in any of the claims of the present application obvious. Nothing in them suggests formulating galathamine or any other acetyl cholinesterase inhibitor in a formulation in which release is delayed so that there is a period in which release of active compound is avoided. Furthermore, there is no motivation to combine the references. Conte's tablets require special production techniques which increase there expense. Those skilled in the art are not going to change from ordinary dosage formulation manufacture to such more complex techniques without a good reason to do so.

In summary, the applicants do not disagree with the examiner that Conte provides a way to produce a programmed release form of acetylcholineaterase inhibitors. What the prior art taken as a whole does not do is teach that there is any reason to use any acetylcholinesterase inhibitors into such a composition because there is nothing in the cited art that gives any reason why such special formulations would provide any benefit for acetylcholinesterase inhibitors. However, even if there were a reason for doing this there is nothing in the art that would point to use of the specific combinations of drug half life and delay that are required by the applicants claims. AS pointed out in the previous response, donepizil, a drug having a half life that is incompatible with the principles underlying the present invention, is the market leader in the treatment of Alzheimer's disease. This , confirms that those skilled in the art had not appreciated the significance of the timing of drug release in the management of Alzheimer's disease and so had no appreciation of the underlying principles of the present invention or of the practical application of those principles that form the subject matter of the claims of the present application.

Therefore, it is respectfully requested that the rejections under 35 USC 103 be withdrawn.

Applicant submits that the present application is in condition for allowance and favorable consideration is respectfully requested.

Respectfully submitted

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